

(43) International Publication Date  
15 September 2005 (15.09.2005)

PCT

(10) International Publication Number  
WO 2005/085243 A2(51) International Patent Classification<sup>7</sup>: C07D 457/00

Budapest (HU). IGNÁCZNÉ SZENDREI, Györgyi [HU/HU]; Zsókvár u. 25., H-1157 Budapest (HU). DEMETER, Ádám [HU/HU]; Gyakorló u. 4/F, H-1106 Budapest (HU).

(21) International Application Number: PCT/HU2005/000022

(74) Common Representative: RICHTER GEDEON VEGYÉSZETI GYÁR RT.; Gyömrői ut 19-21., H-1103 Budapest (HU).

(22) International Filing Date: 2 March 2005 (02.03.2005)

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(25) Filing Language: English

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),

(26) Publication Language: English

[Continued on next page]

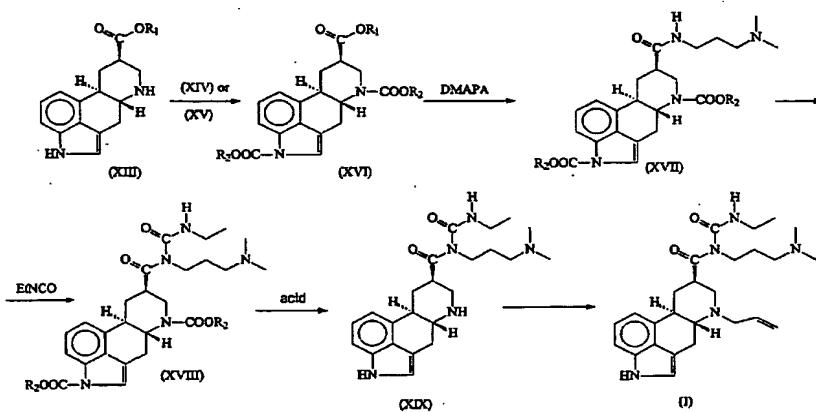
(30) Priority Data:  
P 0400517 4 March 2004 (04.03.2004) HU

(71) Applicant (for all designated States except US): RICHTER GEDEON VEGYÉSZETI GYÁR RT. [HU/HU]; Gyömrői ut 19-21., H-1103 Budapest (HU).

(72) Inventors; and

(75) Inventors/Applicants (for US only): GALAMBOS, János [HU/HU]; Cserkút u. 40., H-1162 Budapest (HU). CZIBULA, László [HU/HU]; Gergely u. 48., H-1103 Budapest (HU). SEBŐK, Ferenc [HU/HU]; Fáy u. 67., H-5800 Mezőkovácsbáza (HU). BÁLINT, Sándorné [HU/HU]; Sasadi út 155., H-1112 Budapest (HU). KASSAI, Ferencné [HU/HU]; Bagomér u. 21/A, H-1188

(54) Title: NOVEL PROCESS FOR PRODUCTION OF CABERGOLINE



(57) **Abstract:** A process for preparing cabergoline (I) from ergoline-8β-carboxylic acid ester (XIII) comprising the following steps. (a) reacting an ergoline-8β-carboxylic acid ester of formula (XIII), wherein R<sub>1</sub> represents a C<sub>1-4</sub> alkyl group, in the presence of a catalyst (i) with a compound of formula (XIV), X-COOR<sub>2</sub> (XIV) wherein R<sub>2</sub> is an optionally substituted straight or branched C<sub>1-6</sub> alkyl group, X represents a bromine or chlorine atom, or (ii) with a compound of formula (XV), O(COOR<sub>2</sub>)<sub>2</sub> (XV) wherein R<sub>2</sub> is a group as defined above; (b) reacting the obtained carbamate derivative of formula (XVI) with 3-(dimethylamino)-propylamine (DMAPA) in the presence of a catalyst; (c) reacting the obtained ergoline-8β-carboxamide derivative of formula (XVII) with ethyl isocyanate (EtNCO) in the presence of ligand(s) and Ib and IIb metal group salt catalysts; (d) reacting the obtained protected N-acylurea derivative of formula (XVIII) with a strong aqueous inorganic acid (aq./acid); (e) reacting the obtained secondary amine (XIX) with an electrophilic allyl alcohol derivative in the presence of a palladium or nickel containing catalyst and optionally in the presence of ligand(s) to form cabergoline (I). The intermediates of (XVI), (XVII), (XVIII) and (XIX) are novel. The polymorphic amorphous form of Cabergoline (I) and the production thereof.

WO 2005/085243 A2



European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Declaration under Rule 4.17:**

- *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA,*

*ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

**Published:**

- *without international search report and to be republished upon receipt of that report*

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*